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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,290	02/02/2004	Yihong Qiu	6437.US.C4	2212

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
08/03/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/770,290	QIU ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 46-59 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 46-59 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6/4/04; 12/22/05
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The receipt is acknowledged of applicants' preliminary amendment and IDS filed 06/04/2004; and supplemental amendment and IDS filed 2/22/2005.

Claims 46-59 are pending and included in the prosecution.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 46-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for oral formulations of specific composition to deliver divalproex sodium, does not reasonably provide enablement for any pharmaceutical formulation comprising any valproate compounds as currently recited by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the

invention; the breadth of the claims; the state of the prior art; the relative skill of those in the art; the amount of direction or guidance presented; the predictability or unpredictability of the art; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention: The nature of the invention as claimed is any pharmaceutical formulation comprising valproate compounds for once a day administration.

The breadth of the claims: The claims are broad. The claims encompass myriad of pharmaceutical formulations including transdermal and parentral formulations comprising any of valproate compounds.

The state of the prior art: The state of the art does not recognize once a day transdermal or parentral formulations comprising any valproate compounds. The state of the art recognizes once a day oral administration of divalproex sodium, see US 4,913,906.

The relative skill of those in the art: The relative skill of those in the art is high.

The amount of direction or guidance presented: The specification provides no guidance, in the way written description, on any formulations other than oral formulation, and provides no guidance of any valproate compounds other than divalproex sodium. In page 13, under the heading "Dosage Forms", applicants stated that:

As noted above, the benefits of this invention are not limited to a single type of dosage form having a particular mechanism of drug release. This enhanced pharmacokinetic profile can

be obtained with any of the oral sustained release dosage forms in use today, following the teachings above. As of the filing date of this application, there are three types of Commonly used oral polymeric controlled release dosage forms. This includes matrix systems, osmotic pumps, and membrane controlled technology (also referred to as reservoir systems).

In example 1, pages 24-31, applicants disclosed very specific oral formulations containing divalproex sodium as shown by table 4 at page 31.

It is not obvious from the disclosure of specific oral formulation comprising specific ingredients in specific amounts containing specific amount of divalproex sodium if other compositions such as transdermal or parentral that are radically differ in their formulations will work to deliver any valproate compound to provide the same effect. The claimed pharmacokinetics are the result of the described specific formulation. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result. A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the formulations fall within the scope of a claim will possess the alleged activity. See *In re Riat et al.* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr et al.* (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The predictability or unpredictability of the art: The lack of guidance from the specification and from the prior art with regard to formulations comprising valproate compounds administered transdermally or parentrally makes practicing the claimed

invention unpredictable in the terms of administering any valproate compounds by the formulation by other routes such as transdermally or parentrally.

The presence or absence of working examples: The specification discloses only very specific oral formulation comprising divalproex sodium, page 10 and example 1. No working examples to show formulations other than the disclosed oral formulation. Therefore, the specification has enabled only oral formulations having specific ingredients to deliver divalproex sodium.

The quantity of experimentation necessary: The art and the specification demonstrate oral formulation of divalproex sodium. Therefor, the practitioner would turn to trial and error experimentation to practice the instant composition for delivering formulation other than oral to deliver valproate compounds without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

3. Claims 46-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amended claims add new matter that is not described in the original specification. Nowhere applicants have disclosed "steady state population", "essentially flat average pharmacokinetic curve such that plasma concentration level vary within a range of about 30 μg/ml". Additionally, claims 49 and

59 recite "one or more dosage units collectively containing the daily does". Recourse to the specification, no support was found.

Further, Applicant did not describe "composition provides a mean steady-state AUC_{0-24} measurement of valproate that is at least 80% of the mean steady-state AUC_{0-24} measurement of valproate provided by an enteric-coated delayed- release divalproex sodium tablet given twice a day". Applicants did not describe "composition provides a mean steady-state C_{max} of valproate that is statistically significantly lower than the mean steady-state C_{max} of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day". Applicants did not describe "composition having mean steady-state degree of fluctuation of valproate less than the mean steady-state degree of fluctuation of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day". Applicants did not describe "composition having mean steady-state T_{max} of valproate at least twice as long as the mean steady-state T_{max} of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day". Applicants did not describe "composition having mean steady-state C_{min} of valproate is not statistically different than the mean steady- state C_{min} of valproate provided by the enteric-coated delayed-release divalproex sodium tablet given twice a day". The claimed comparison data with enteric-coated delayed-release divalproex sodium tablet given twice a day does not convey to one of ordinary skill in the art that applicants were in possession of the claimed subject matter. The functional comparative language is recited without any correlation does not meet the written description requirement as one of ordinary skill in the art could not recognize or

understand the claims from the mere recitation of the function and comparison. The claimed pharmacokinetics are the result of combination of the ingredients and their ratios in formulation including the drug, carrier, and different excipients. Claims employing functional language at the point of novelty, such as applicants', neither provide those elements required to practice the inventions, nor "inform the public" during the life of the patent of the limits of the monopoly asserted.

To satisfy the Written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that applicant were in possession of the claimed invention. *Vas-Cath Inc. v Mahurkar*, 19 USPQ 2d 1111. The invention is, for purpose of the "written description" inquiry, what ever is now claimed (see page 1117). The specification does not clearly allow person of ordinary skill in the art to recognize that [he or she] invented what is claimed (see *Vas-Cath* at page 116). One cannot describe what one has not conceived. See *Fiddes v Baird*, 30 USPQ2d 1481, 1483.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 46-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The expressions "essentially flat average" and "at least" recited by the claims are relative terms which renders the claim indefinite. The term is not defined by the claim, and the specification does not provide a standard for

ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably recognize of the scope of the invention.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 46-59 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,419,953. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed pharmacokinetics are inherent.

8. Claims 46-57 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,511,678. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed pharmacokinetics are inherent.

9. Claims 46-59 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,528,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed pharmacokinetics are inherent.

10. Claims 46-59 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,528,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed pharmacokinetics are inherent.

11. Claims 46-59 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,720,004. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed pharmacokinetics are inherent.

12. Claims 46-59 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,713,086. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of the issued patent are directed to formulation comprising valproate compounds. The issued claims anticipate the present claims since the presently claimed pharmacokinetics are inherent.

13. Claims 46-59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16 and 19 of copending Application No. 10/770.291. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the referenced copending applications and would be covered by any patent granted on the copending applications since the referenced copending applications and the instant application are claiming common subject matter as follows: formulation comprising valproate compounds. The present

claims and the conflicting claims in the copending application anticipate each other since pharmacokinetics are inherent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 46-59 are rejected under 35 U.S.C. 102(b) as being anticipated by article "EPILIMCHRONO: A MULTIDOSE, CROSSOVER COMPARISON OF TWO FORMULATIONS OF VALPROATE IN HEALTHY VOLUNTEERS", by Roberts et al.

> The present claims are directed to pharmaceutical composition comprising valproate compounds administered once a day, claims 46 and 56, or more than one time a day, claims 49 and 59.

Roberts et al. disclosed once a day controlled release formulation to deliver divalproex sodium. Roberts et al. provided comparison between once a day formulation and twice daily controlled formulation, either enteric coated or not. The comparison showed once a day formulation of 1000 mg is almost identical to the enteric coated twice a day formulation regarding AUC (0-24 hr), which read on the claimed range of at

least 80% (claim 51). The reference disclosed lower mean C_{max} of once a day formulation than twice a day enteric coated formulation. Table 2 showed that C_{min} was not significantly different in once a day formulation and twice a day enteric coated formulation. Regarding T_{max}, it was longest with once a day formulation than twice a day enteric coated formulation. The enteric coated twice a day formulation showed larger fluctuation than once a day formulation. The variation in the plasma concentration is inherent to a specific formulation.

16. Claims 46-59 are rejected under 35 U.S.C. 102(b) as being anticipated by US 4,913,906 (906).

US '906 disclosed composition for controlled release of salts of valproic acid comprising 10-80% of the active agent (abstract; col.2, lines 1-10, 63-68). The controlled release formulation results in sustained action of the drug with small fluctuation of the plasma level over prolonged period of time (col.1, lines 59-62). The composition is a once a day oral formulation that delivers the drug for 24 hour and shows about 97% dissolution rate profile after 24 hr. (col. 5 and 6, tables 1-4). Divalproex sodium is disclosed as one of the salts of valproic acid suitable for the formulation of the reference (col.5, lines 15-20). The pharmacokinetics are inherent for the formulation. In absence of claiming a specific formulation, the prior art anticipated the claims.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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